A STUDY OF PREGNANCY IN WOMEN WITH EPILEPSY

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations

for the award of the degree of

M.D. BRANCH - I

GENERAL MEDICINE

GOVT. STANLEY MEDICAL COLLEGE & HOSPITAL
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI, INDIA

MARCH 2009

CERTIFICATE

This is to certify that the dissertation titled **"A STUDY OF PREGNANCY IN WOMEN WITH EPILEPSY"** is the bonafide original work of **Dr. SAMANTHA S,** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in MARCH 2009. The Period of study was from 2007 – 2008.

PROF V. RUCKMANI, M.D.,
Professor and Head
Department of Medicine
Govt. Stanley Medical College
and Hospital
Chennai 600 001

PROF. S. RAMASAMY, M.D.,
Professor of Medicine
Govt. Stanley Medical College
and Hospital
Chennai 600 001

Dr. J. MOHANASUNDARAM, M.D., Ph.D., DNB
D E A N
Government Stanley Medical College and Hospital
Chennai – 600 001

DECLARATION

I, **Dr. SAMANTHA S,** solemnly declare that the dissertation titled, "**A STUDY OF PREGNANCY IN WOMEN WITH EPILEPSY"** was done by me at Government Stanley hospital during 2007 – 2008 under the guidance and supervision of my unit Chief **Prof. S. RAMASAMY, M.D.,** Professor of Therapeutics, Government Stanley Medical College and Hospital, Chennai.

The dissertation is submitted to the Tamilnadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of MD Degree (Branch-1) in General Medicine.

Place: Chennai **(Dr. SAMANTHA S)**

Date :

ACKNOWLEDGEMENT

I thank **Dr. J. MOHANASUNDARAM, M.D., Ph.D., DNB** Dean, Government Stanley Medical College and Hospital for permitting me to use all the resources at his disposal for my dissertation.

I am grateful to **Prof.V.RUCKMANI, M.D.,** Professor and Head of the Department of Medicine, Stanley Medical College and Hospital for permitting me to do the study.

I thank **Prof.S.RAMASAMY, M.D.,** Professor of Therapeutics and Chief of medical unit II, Stanley Medical College and Hospital for approving this study and giving valuable suggestions in preparing this dissertation.

I express my particular thanks to **Prof.A.MURUGESAN, M.D., DM**, Head of the Department of Neuro Medicine for allowing me to utilize the epilepsy clinic. I also thank him for his invaluable guidance.

I am extremely thankful to my assistant professors **Dr. S.ASHOK KUMAR, M.D.,** and **Dr.S.GEETHA, M.D.,** for their valuable help and encouragement.

I express my gratitude to **Dr.R.LAKSHMINARASIMHAN, M.D., D.M.,** Professor of neurology, Government Medical College, Vellore for his valuable guidance and support.

My sincere thanks to the Assistant Professors of the department of Neuro Medicine **Dr.V.C.CHANDRAMOULI, M.D.,D.M.,** and **Dr.A.GUNASEKAR, M.D., D.M.,** for their guidance and constant encouragement.

Finally, I wish to thank all the patients included in this study and my colleagues for their cooperation and support.

CONTENTS

INTRODUCTION

Epilepsy is recognized as the commonest serious neurological disorder in the world. Women with epilepsy (WWE) experience several gender-related physical and social problems. They constitute high obstetric risk because of reduced fertility, risk of seizures during pregnancy, and complications of pregnancy. Hormonal and other factors can alter the pharmacokinetics of antiepileptic drugs (AED) during pregnancy and puerperium. Antenatal exposure to AEDs, particularly at higher dosage and in polytherapy, increases the risk of fetal malformation. Recent reports raise the possibility of selective developmental language deficits and neurocognitive deficits with antenatal exposure to AEDs.

Epilepsy and antiepileptic therapy therefore affects both maternal and fetal well being. Seizure type as well as AEDs used have an effect on the course and outcome of pregnancy. Conversely, pregnancy affects seizure control and the pharmacokinetics of AEDs. The management of a woman with epilepsy during her pregnancy thus presents a major therapeutic challenge to the treating physician.

AIMS OF THE STUDY

This study analyzes the incidence of various maternal & foetal outcomes occurring in pregnant women with epilepsy.

Maternal outcomes

1. Primary outcomes : abortions, IUD, live births, maternal mortality
2. Secondary outcomes : Mode of delivery

   Seizures during pregnancy and delivery

Foetal outcomes

1. Primary outcome : Congenital malformations
2. Secondary outcomes : Infant mortality, growth retardation

REVIEW OF LITERATURE

Epilepsy is a common neurological disorder with a prevalence rate of approximately 0.5% in most communities. It is estimated that there are over 2.5 million women with epilepsy (WWE) in India, with up to 52% of them being in the reproductive age group. People with epilepsy, especially women, experience tremendous social stigma and alienation in life[2]. Neurologists, Physicians and obstetricians are increasingly faced with WWE during pregnancy, but are not adequately informed about their optimal management.

Several important aspects need to be attended to, while managing pregnancy in WWE: Pregnancy influences the natural history of epilepsy and seizure frequency is likely to change; the bioavailability of antiepileptic drugs (AEDs) may change considerably owing to alterations in its pharmacodynamics and kinetics. Both epilepsy as well as AED therapy may have an impact on outcome and mode of termination of pregnancy. Most importantly AEDs are potentially teratogenic and hence may increase the risk of fetal malformations.Psychomotor retardation in the offspring is also a concern in women with epilepsy[1].

EFFECT OF PREGNANCY ON EPILEPSY

Hormonal aspects of epilepsy

Experimental and clinical studies have shown that seizures are influenced by the female sex hormones estrogen and progesterone. In general, estrogen lowers the seizure threshold and progesterone elevates it. In most experimental animal models, estrogen lowers the threshold for seizures induced by electroshock, kindling, pentylenetetrazol, and other agents. Progesterone, on the other hand, reduces spontaneous and induced epileptiform discharges. Similar observations have been made in human beings also[7].

Effect of pregnancy on seizure frequency

Pregnancy has a variable effect on seizure frequency. Seizure frequency may remain unchanged or decreases in two-third of WWE, whereas it may increase in others. Seizure frequency may also vary between pregnancies in the same woman. There can be diverse patterns of seizure frequency during pregnancy. WWE may have a stable pattern with seizure frequency remaining more, less, or unchanged throughout the entire period of pregnancy. Others may have an unstable pattern wherein the seizure frequency may vary widely and often unpredictably during different months

of pregnancy. In a recent study it was observed that nearly 61% patients had a stable pattern and 39% women had an unstable pattern[7,10].

In most studies, seizure frequency has been observed to increase in about one third of the patients. While rare isolated seizures carry uncertain risks, uncontrolled convulsive seizures place both mother and baby at risk, increased risk of injury or other complications of seizures in the mother, and increased risk of bradycardia, placental abruption, premature labor, intracranial hemorrhage, or even fetal death in the baby; this risk is particularly high if seizures progress to status epilepticus. Effects of nonconvulsive seizures on developing fetuses are not well documented.

Diverse mechanisms have been put forward to explain the change in seizure frequency during pregnancy. Apart from the reproductive hormones, several other factors such as noncompliance and decrease in blood levels of free form of AED, influence seizures during pregnancy. Increased stress and sleep deprivation may contribute. Physiologic changes of pregnancy that may alter seizure threshold include increase in sex hormone levels and sodium and water retention. Altered physiology of pregnancy also can change previously stable AED levels owing to changes in absorption (either through gastric motility changes or nausea and vomiting), changes in volume of distribution, alterations in protein binding, and increase in hepatic

metabolism. Providers also must be sensitive to the possibility that lower AED levels reflect noncompliance with medication due to fear of teratogenic effects[1].

Another factor to be noted is that women who have poorly controlled seizures even before pregnancy, have a higher incidence of seizures during pregnancy[23].

AED levels should be monitored more closely than usual during pregnancy. Pharmacokinetic changes demand monitoring of free levels of highly protein bound AEDs to avoid confusion with increased seizures (or symptoms of toxicity) despite therapeutic total serum drug levels.

EFFECT OF EPILEPSY ON PREGNANCY

Infertility

It is generally considered that women with epilepsy have reduced fertility rate.This is explained by a number of reasons usually acting in concert in each individual case[4].

The proportion of women who get married and the age at marriage can influence the fertility rate. The demographic, social, economic, and medical factors that influence marriage in women with epilepsy need further examination[2].

Polycystic ovarian disease (PCOD), an important cause for infertility, may occur in approximately 10% of women in the community. It should be distinguished from polycystic ovaries that may be seen in as much as 20% of women in the community. The European-American consensus workshop requires two of the three criteria (oligo/anovulaton, clinical, or biochemical signs of hyperandrogenism and polycystic ovaries) to be present in order to diagnose PCOD. It appears that women with epilepsy have an increased tendency for PCOD.

Use of sodium valproate had been shown to correlate with the presence of PCOD, which reverses when valproate is substituted by another AED[9]. A recent consensus report has recommended that if a reproductive endocrine disorder is found, AED treatment should be reviewed to ensure that it is correct for the particular seizure type and that it is not contributing to the endocrine problem. The possible benefits of a change in treatment must be balanced against seizure control and the cumulative side effect of alternative agents[5].

Complications of pregnancy

It is uncertain whether women with epilepsy have more complications of pregnancy. Several studies have shown a higher frequency of the following complications. But these findings have not been validated by all studies.

1) Pre eclampsia
2) Eclampsia
3) Abruptio placenta
4) Spontaneous abortion

Frequency of cesarean section may be increased for women with epilepsy, although most of them can have normal vaginal delivery. Uterine

inertia, seizures, and failure of progression of labor are usual causes of cesarian section .Frequency of induced labor is also higher[28].

Indications for cesarean section

Elective cesarean section

Poor control of seizures

Intrapartum seizures

Substantial neurological or mental retardation

Uterine inertia

Failure of induction of labor

Heavy sedation for patient

Fetal asphyxia

Effects of maternal seizures on the fetus

Seizures, especially in late gestation and delivery,may adversely affect the fetus by causing autonomic, metabolic and direct traumatic effects.

A generalized seizure at term can cause transient fetal asphyxia secondary to maternal hypoxia and placental insufficiency. Fetal bradycardia, reduced variability, and decelerations indicating fetal distress are seen for approximately 15 min after grand mal seizure.

Generalized seizures can also cause direct fetal trauma leading on to consequences like intracranial hemorrhage.

There is no evidence that nonconvulsive seizure affects the fetus adversely[13].

EFFECT OF EPILEPSY AND AED ON FOETUS

Effects on fetal and neonatal anthropometric parameters

Minor variations in anthropometric features have been observed in infants of mothers with epilepsy[26]. Low birth weight and reduced length and head circumference have been observed in certain studies. A recent study has shown that infants exposed to AEDs may have increased tendency for minor facial anthropometric variations when compared to normal babies. However, this variation was not correlated with any specific AED or with polytherapy compared with monotherapy[5].

Physiological impairments that were noticed in the newborns include low Apgar score and failure to thrive. Babies born to mothers taking phenobarbitone may experience mild irritability owing to the withdrawal effect of phenobarbitone, but it is likely to disappear in a few days' time. Rarely, withdrawal seizures have been noticed in exposed neonates[6].

Malformations

The risk of malformation in the baby is one of the major concerns for women with epilepsy. Deviations from normal development can be classified into major malformations and minor anomalies.

Malformations refer to major abnormalities that require surgical intervention within the first year of life or are likely to result in significant impairment and disability, e.g., neural tube defects (NTDs), congenital heart disease, or cleft palate. Anomalies are minor deviations from normal development that may not cause significant impairment or disability, e.g., Hypertelorism, acral hypoplasia of nails.

In 1964, Janz first drew attention to the possible teratogenic effects of AED's. Since then several fetal syndromes such as fetal hydantoin syndrome, fetal ethosuximide syndrome and fetal phenobarbitone syndrome have been described. The commonly observed malformations may affect cardiovascular system, gastrointestinal system, skeletal and connective tissues, and central nervous system. It had been observed that the malformations observed with different AEDs share much in common and are often indistinguishable. Hence, they are often referred to as fetal AED syndromes[24].

Phenytoin

Phenytoin is the oldest nonsedative antiseizure drug, introduced in 1938.

Mechanism of action: Phenytoin is a diphenyl substituted hydantoin. It has major effects on several physiological systems. It alters sodium, potassium and calcium conductance , membrane potentials and the concentrations of amino acids and neurotransmitters norepinephrine, acetylcholine and GABA.

Studies with neurons show that phenytoin blocks sustained high frequency repetitive firing of action potentials. It is a use dependant effect on sodium conductance, arising from preferential binding to and prolongation of the inactive state of the sodium channel. This effect is seen at therapeutically relevant concentrations. The drug also interacts with membrane lipids and this might promote stabilization of membranes[36].

Pharmacokinetics: Absorption is highly dependant on the formulation of the dosage form. Absorption from gastrointestinal tract is nearly complete though the time to peak values may range from three to twelve hours. Phenytoin is highly bound to plasma proteins. The half life of phenytoin varies from 12 to 36 hours, with an average of 24 hours for most patients. It may take 5 to 7 days to reach steady state blood levels after each dosage

change. Phenytoin is metabolized by the liver, at low blood levels metabolism follows first order kinetics. But as therapeutic levels are reached metabolism is saturable[36].

Therapeutic levels and dosage: The therapeutic plasma level of phenytoin for most patients is between 10 and 20μg/ml. When oral therapy is started it is common to begin most adults at a dose of 200 to 300mg/day. If seizures continue higher doses are usually necessary to achieve plasma levels in the upper therapeutic range. Because of its dose dependant kinetics some toxicity may occur with only small increments in dose.

Drug interactions: They are primarily related to protein binding or to metabolism. Since phenytoin is 90% bound to plasma protein changes in protein levels will affect total drug levels. Phenytoin has been shown to induce microsomal enzymes responsible for the metabolism of a number of drugs. Other anti epileptic drugs notably phenobarbitone and carbamazepine decrease steady state concentrations of phenytoin through hepatic microsomal enzyme induction. On the other hand drugs like isoniazid inhibit the metabolism of phenytoin and increase drug levels.

Adverse effects: Higher doses can cause several neurological manifestations like nystagmus, diplopia, ataxia and peripheral neuropathy. Gingival hyperplasia and hirsutism occur to some degree in most patients. Chronic

use also results in abnormalities in vitamin D metabolism and osteomalacia. Idiosyncratic reactions like skin rash and agranulocytosis may also be seen.

Use of phenytoin in pregnant women is associated with increased risks of both minor and major malformations in the foetus. Phenytoin is particularly associated with an increased risk of cleft lip and palate as well as dysmorphic features such as nail and distal phalangeal hypoplasia and craniofacial abnormalities[25] .

Phenobarbitone

Phenobarbitone is the oldest of the currently available anti epileptic drugs and is still widely used in India. Although it has long been considered one of the safest of the antiseizure agents, the use of other medications with less sedative effects has been urged.

Mechanism of action: Phenobarbitone enhances inhibitory processes and diminishes excitatory transmission. It binds to an allosteric regulatory site on the GABA-benzodiazepine receptor, and it enhances the GABA receptor mediated current by prolonging the opening of chloride channels. It also blocks excitatory responses induced by glutamate, principally those mediated by the action of the AMPA receptor. At high concentrations phenobarbitone suppresses high frequency repetitive firing in neurons[36].

Pharmacokinetics: Phenobarbitone has a slow oral absorption and a long plasma half life of 80 to 120 hours. Steady state concentrations are reached in two to three weeks and a single daily dose can be used for maintenance. Phenobarbitone is 20% plasma protein bound. It crosses the placenta and is secreted in milk, can produce effects on the foetus and the suckling infant. It is metabolized by the liver and excreted by the kidney.

Therapeutic levels and dosage: Therapeutic levels inn most patients range from 10 to 40μg/ml. It is usually used in a dose of 60mg one to three times a day in adults.

Clinical use: It is useful in the treatment of generalized tonic clonic seizures, though the drug is virtually tried for every seizure type especially when attacks are difficult to control. Its most well documented use is in febrile seizures.

Drug interactions and toxicity: Barbiturates induce the metabolism of several drugs and reduce their effectiveness – warfarin, steroids, tolbutamide, theophylline. It also has interactions with other anti epileptic drugs. Valproate increases concentrations of phenobarbitone.

Phenobarbitone has been associated with congenital heart defects, facial clefts, and a specific pattern of minor anomalies and dysmorphic features[5].

Sodium valproate

Sodium valproate, also used as the free acid, valproic acid, was found to have anti seizure activity when it was used as a solvent in search of other agents effective against seizures. Valproic acid is fully ionized at body ph, and for that reason the active form of the drug may be assumed to be the valproate ion regardless of whether valproic acid or a salt of the acid is administered .

Mechanism of action: valproate is active against both pentylenetetrazol and maximal electroshock seizures. It blocks sustained high frequency repetitive firing of neurons at therapeutic concentrations. Valproate owes its broad spectrum of activity to more than one molecular mechanism. It prolong sodium channel inactivation. It augments release of inhibitory transmitter GABA, at higher concentrations it also inhibits GABA degradation. In addition it also has an ethosuximide like action, in that it suppresses calcium mediated 'T' current[36].

Pharmacokinetics: Valproate is well absorbed following an oral dose, with bioavailability greater than 80%. Peak blood levels are observed within two hours. The drug is also 90% bound to plasma proteins. Since valprote is both highly ionized as well as protein bound, its distribution is essentially confined to extracellular water, with a volume of distribution of

approximately 0.15l/kg. its half life varies from 9 to 18 hours. It is metabolized in the liver by oxidation and glucuronide conjugation and excreted in urine[36].

Therapeutic levels and dosage: dosages of 25 to 30mg/kg/day may be adequate in some patients, but others may require up to 60mg/kg. therapeutic levels of valproate range from 50 to 100µg/ml.

Clinical use: Valproate has a very broad spectrum of action. It is a first line drug for GTCS, simple and complex partial seizures as well as absence seizures. Valproate is unique in its ability to control certain types of myoclonic seizures. A few patients with atonic attacks may also respond. Other uses of valproate include management of bipolar disorder and migraine prophylaxis.

Drug interactions: Valproate inhibits the metabolism of several drugs, including phenobarbitone, phenytoin and carbamazepine leading to higher steady state concentrations of these agents. Valproate also displaces phenytoin from plasma proteins[9].

Toxicity: The most common dose related adverse effects of valproate are nausea, vomiting and other gastrointestinal complaints. A fine tremor is frequently seen at higher doses. Other reversible adverse effects include weight gain, increased appetite and hair loss. The idiosyncratic toxicity of

valproate is largely limited to hepatotoxicity which may be severe. Valproate in pregnancy has been associated with a 1–2% risk of neural tube defects. Some studies have suggested that daily doses of valproate greater than 1,000 mg/day carry a greater risk of spina bifida and other malformations possibly due to high peak serum concentrations of valproate. Three or four times daily treatment or slow-release preparations may minimize this risk by reducing peak plasma levels, although the UK pregnancy database has failed to show any benefit of a slow-release formulation. There is also an increased incidence of cardiovascular and urogenital malformations. Thus, although valproate is a very effective drug for women with generalized epilepsies, the risks and benefits should be carefully considered[20] .

Carbamazepine

Chemically related to imipramine, carbamazepine is a tricyclic compound initially introduced for the treatment of trigeminal neuralgia.

Mechanism of action: The mechanism of action appears to be similar to that of phenytoin. It blocks sodium channels at therapeutic concentrations and inhibits high frequency repetitive firing in neurons. It also acts presynaptically to decrease synaptic transmission. Carbamazepine also inhibits uptake and release of norepinephrine from brain synaptosomes .

Pharmacokinetics: The rate of absorption of carbamazepine varies widely in different patients. Peak levels are usually achieved 6 to 8 hours after administration. The drug is only 70% protein bound, no displacement of other drugs from protein binding sites has been observed. The drug also has the ability to induce microsomal enzymes. It induces its own metabolism and the half life decreases to about 20 hours in long term users.

Therapeutic levels and dosage: In adults a daily dose of 1 to 2 grams is used. Therapeutic levels are usually between 4 to 8μg/ml.

Clinical use: It is considered the drug of choice for partial seizures. It is also one of the first line drugs for GTCS. Other uses include trigeminal neuralgia and bipolar disorder[36].

Drug interactions: Drug interactions involving carbamazepine are almost entirely related to the drugs enzyme inducing properties. Induction of hepatic enzymes may cause a reduction in the steady state concentration of carbamezepine itself and an increased rate of metabolism of primidone, phenytoin, ethosuximide, valproate and clonazepam. No clinically significant protein binding interactions have been reported[10].

Toxicity: The most common dose related adverse effects are diplopia and ataxia. Hyponatremia and water intoxication have occasionally occurred.

Idiosyncratic blood dyscrasias like aplastic anemia and agranulocytosis have also been observed. Hepatic dysfunction is rarely seen.

The risk of congenital malformations with carbamazepine monotherapy is similar to that of most other anti epileptic dugs. In one study, there was a 0.9% reported risk of neural tube defects in the offspring of mothers who took carbamazepine through pregnancy . There have also been reports of reduced head circumference at birth, developmental delay, and dysmorphic features .

Lamotrigine

The indications for the use of this drug are similar to those for use of valproate. The incidence of major malformations with this drug is lower than with valproate. The UK and Australian pregnancy databases currently suggest that the risk of fetal malformations with lamotrigine monotherapy is similar to that of carbamazepine. Persons on LTG may experience increase in seizure frequency during pregnancy because LTG is eliminated much faster than during non pregnant state[17].

There are not yet enough monotherapy pregnancies with any of the other newer AEDs to be able to accurately advise women, although a recent review of oxcarbazepine does not appear to show an increased risk or any

specific pattern of malformations. Both topiramate and zonisamideare teratogenic in animal studies[40].

AED's and teratogenecity

The report of 'foetal hydantoin syndrome' was first published in 1960s. Since then many aspects of drug toxicity in the foetus have been reported, the salient points being that:

a) Infants of mothers with epilepsy are at greater risk of developing congenital malformations than general population.

b) Foetal malformations among infants born to mothers with epilepsy on AEDs during pregnancy are higher than among infants of epileptic mothers not exposed to AEDs in-utero.

c) Mean serum AED level is higher in mothers of infants with malformation.

d) Infants of mothers on polytherapy have higher rates of malformations[4].

Major malformations are defined as defects of medical, surgical or cosmetic importance. This type of anomaly, which will seriously affect a child's life, occurs in 2 to 3 percent of all liveborn children. Types of major malformations occurring most often in children of women with epilepsy are orofacial clefts, cardiac abnormalities and neural tube defects. The incidence

of minor physical defects in infants born to women with epilepsy is approximately 15 percent. Features such as hypertelorism, epicanthal folds, shallow philtrum, distal digital hypoplasia, and simian creases are examples of minor congenital malformations. Although the incidence is reported as 2 to 3 times greater in women with epilepsy, these may be present in infants whose mothers use other types of medication or have excessive alcohol intake during pregnancy. These anomalies do not cause any serious problems and are primarily of cosmetic concern[3].

Studies suggest that the risk of significant fetal malformation is approximately 3% if one AED is taken (slightly above the background risk) and up to 17 % if two or more AEDs are taken . Most major malformations develop at an early stage in pregnancy, often before the woman knows she is pregnant[2]. AED exposure in the later stages of pregnancy may still lead to minor morphological abnormalities or specific learning difficulties (particularly in association with valproate sodium therapy). The mechanisms whereby AEDs are teratogenic have not been definitely established. Recent pregnancy databases have suggested that valproate is significantly more teratogenic than carbamazepine, and the combination of valproate sodium and lamotrigine is particularly teratogenic.In a recent study the rate of major congenital malformations was 2.4% in women with epilepsy not taking

AED's, 3.4% on monotherapy, 6.5% on polytherapy. In the same study monotherapy associated major malformations rate was 2.3% for carbamezipine, 2.1% for lamotrigine and 5.9% for sodium valproate. Valproic acid is the only AED for which a dose dependency has been confirmed in several studies, the increase in risk of major congenital malformations compared with other AED's is especially evident at doses above 800-1000 mg/day[5].

The extent of the causal relationship with AEDs has been questioned, and evidence has been put forward for maternal genetic factors influencing the development of minor abnormalities such as epicanthus and micrognathia. Larger prospective studies of women treated with monotherapy are necessary to resolve these issues[1].

Neurocognitive development and AED exposure in-utero

Most babies born to women with epilepsy are normal. Recent reports suggest that these babies may have an increased risk of developmental delay or specific learning disabilities. Factors other than the maternal epilepsy that are thought to be important are IQ scores in the mother and AED polypharmacy (particularly exposure to phenobarbital in utero). Further studies are needed for validation of these reports[16].

MANAGEMENT OF PREGNANCY IN EPILEPSY

Preconceptional management

Preconceptional evaluation is the most important phase in the management of epilepsy and pregnancy. Women with epilepsy need to have a neurological review at this stage, in order to ascertain the diagnosis and the need for continued treatment with AEDs. Several professional groups have examined this aspect in great detail and have come out with evidence based practice guidelines[2,4].

Most studies have shown that the risk of malformations in fetus is likely to be low with monotherapy, use of relatively lower dose, spacing of daily dose into multiple aliquots, and preconception use of folic acid. The controlled or extended release formulations of AEDs are likely to maintain a steady blood levels without much fluctuations. There is considerable variation in the risk of malformations with different AEDs even when used as monotherapy. Different AEDs carry different therapeutic efficacies against different seizure types. It may be possible to withdraw AED if the patient had remained seizure-free for more than 2 years. The general guidelines for AED withdrawal as for patients in remission are followed in WWE also. Persons with juvenile myoclonic epilepsy may have to continue therapy, even when they had been seizure-free for quite some time and the

EEG was normal. In the case of high-risk pregnancies (with family history of NTDs or previous pregnancies with birth defects), the option of an alternate AED needs to be discussed with the patients although the second AED may also carry the potential risk. There is much debate regarding the choice of AED for women with juvenile myoclonic epilepsy who are contemplating pregnancy. The risk and benefits of VPA vs LTG or TPM needs to be discussed with them so that the patients would be able to make an informed choice. High-dosage VPA and combination of VPA and LTG may be avoided, if possible, in preconception period and early pregnancy[4].

A universal recommendation for antenatal care includes prescription of 0.4 mg of folic acid daily[19]. The dosage of folic acid recommended for women with higher risk varies from 1–4 mg daily in several countries. Women in developing countries may be at higher risk of folic acid deficiency owing to dietary inadequacy, infections, or concomitant use of other drugs. In India, 5-mg tablets of folic acid are readily available. It is therefore recommended that all women planning pregnancy should receive 5 mg daily of folic acid. The general protocol for preconception management of WWE that is followed in the Indian Registry of Epilepsy and Pregnancy (IREP) is depicted[2] .

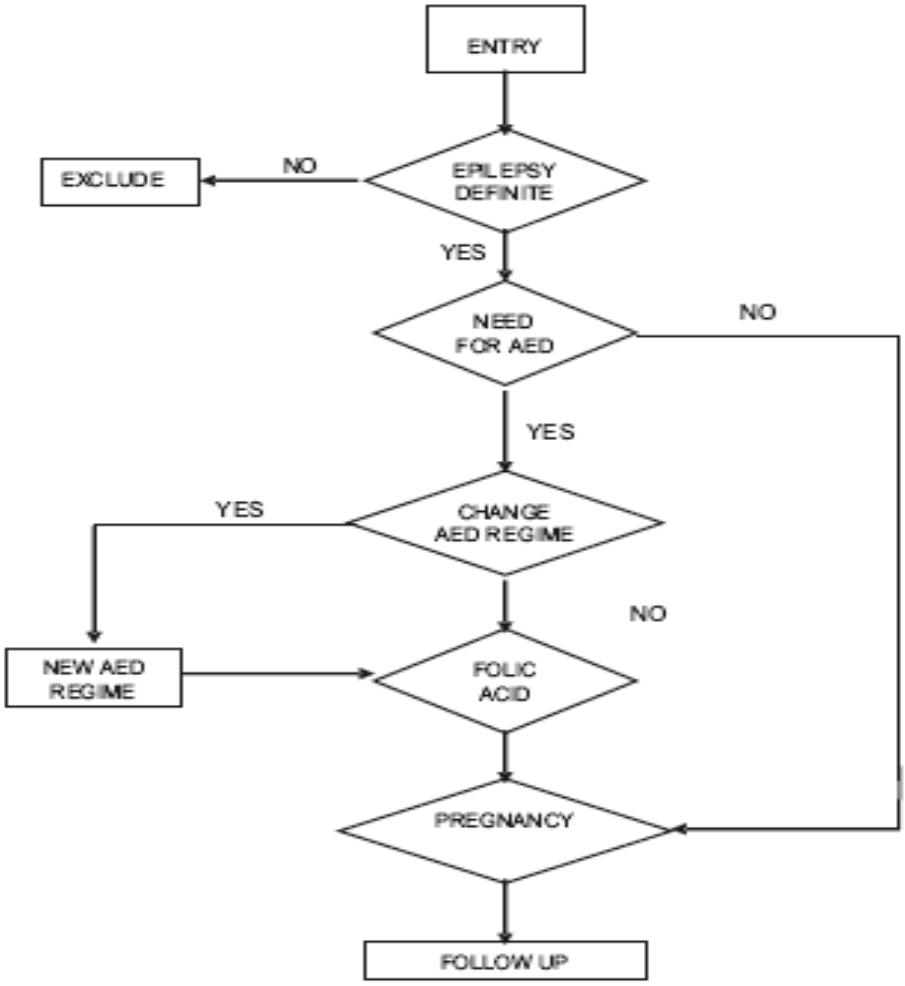


Figure 1: Algorithm for the management of epilepsy and pregnancy

Management of epilepsy during pregnancy

Seizures tend to improve or remain unchanged in nearly two thirds of women with epilepsy. The risk of seizures is higher in the first trimester of pregnancy and around delivery time. The policy of the IREP is to avoid any change in AEDs once pregnancy had been confirmed. Nevertheless, in cases of polytherapy with multiple drugs, it may be possible to eliminate the third,

and occasionally the second, AED after retaining the AED(s) appropriate for the seizure. It is preferable to keep the total daily dose of VPA below 1000 mg as higher doses have been implicated with an increased risk of NTD(18). Care should be taken to split the daily dose in to three or four divided aliquots in order to avoid high peak levels in the blood. It is important to ensure good compliance with AEDs throughout pregnancy in order to avoid relapse of seizures. The dosage may have to be increased in some patients in the third trimester, especially if the blood levels (preferably free drug levels) are low. The risk of seizure relapse around the time of delivery is three times more than during the rest of the pregnancy. The increased risk of seizure relapse is probably related to the lack of compliance, dehydration, prolonged fasting, or effect of concomitant medications. Care should be taken to avoid such provoking factors at the time of delivery. Status epilepticus can occur rarely during pregnancy (less than one percent). General guidelines for managing SE can be followed in such instances. The fetal outcome had been poor when it took a long time to control seizures[2].

Follow up in pregnancy

The general schedule of antenatal check-up should be followed in all WWE. Folic acid supplementation should be initiated as soon as pregnancy is confirmed, if it had not been started in the preconception period[2].

Monitoring for fetal malformations

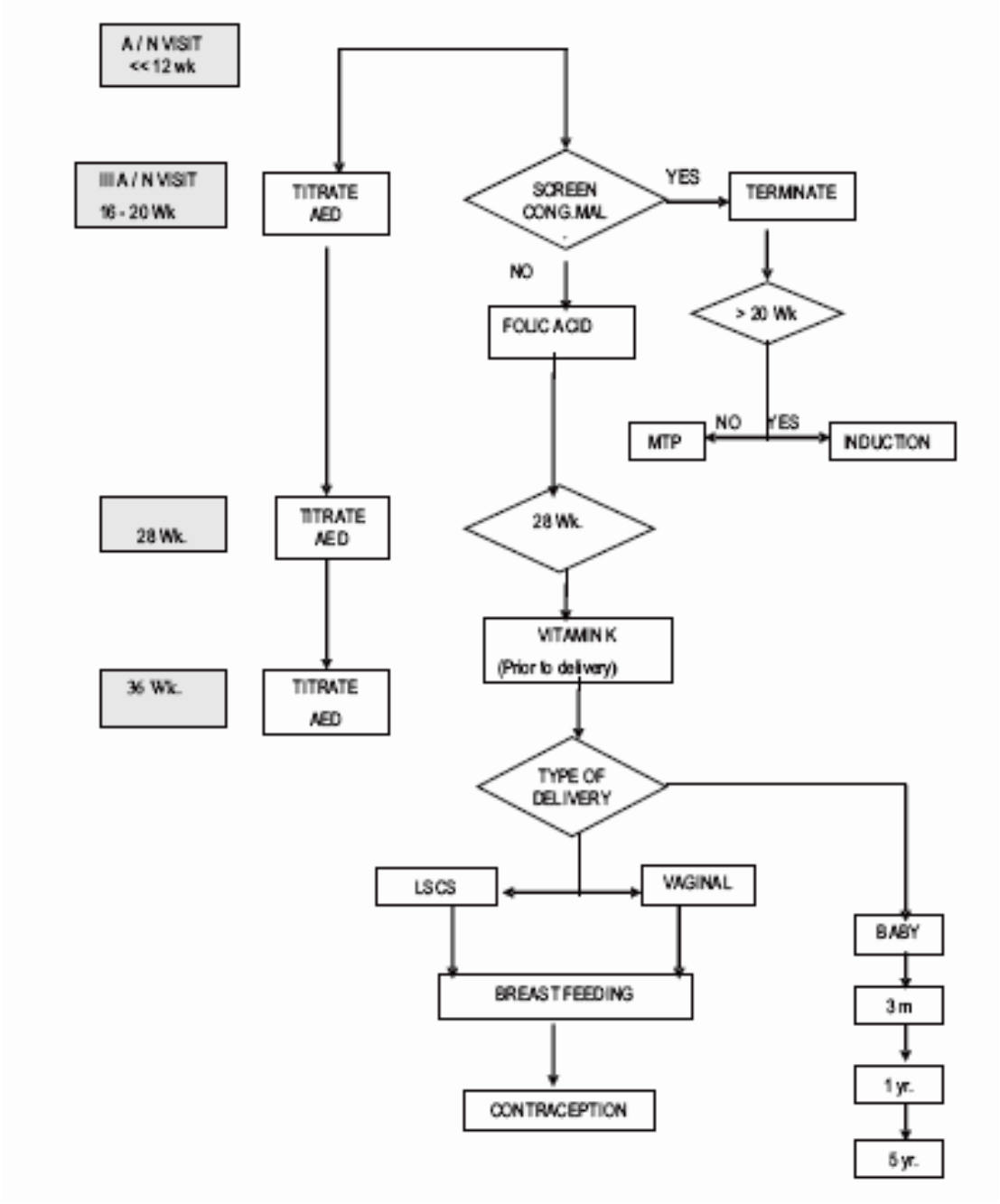
Monitoring for fetal malformations should be carried out towards the end of first trimester. Biochemical screening in the form of serum AFP levels as well as radiological screening using ultrasound is begun by about the 12^{th} - 14^{th} week of gestation.

The first line screening procedure would be estimation of serum α-feto-protein (AFP), which tends to be elevated in cases of open NTD. Serum levels of AFP increase gradually during the first trimester and drop toward the fourth month of pregnancy. Hence, the levels should be correlated with the period of pregnancy preferably with conceptual age, calculated with the help of ultrasonography. A recent trend is to express the AFP level as multiples of medians for that period of pregnancy[37]. This makes interlaboratory comparisons easier. AFP levels could be elevated for other reasons such as twin pregnancy, placental hemorrhage, etc. If the AFP levels are abnormally elevated, the trend needs to be ascertained by repeating the test after 1 or 2 weeks. The result also needs to be correlated with a detailed ultrasonography targeting fetal organogenesis. The management protocol that is followed in the IREP is given in Figure 2.

Of late, ultrasonography that can detect several fetal malformations has become an integral part of antenatal check. Early detection of malformations such as spina bifida and meningomyelocele require careful ultrasonography by experienced persons. Amniocentesis and cord blood analysis may have to be resorted to in selected cases where fetal karyotyping also may be required[38].

Vitamin K prophylaxis

Hemorrhagic disease of the newborn is more likely to occur in infants whose mothers are taking hepatic microsomal enzyme-inducing AEDs . A dose of 20 mg/day of vitamin K should be given daily orally in the last month of pregnancy to these mothers. Infants should receive 1mg of vitamin K intramuscularly at birth[2,4] .



IREP algorithm for follow up during pregnancy : Fig 2

Postpartum Management

The AEDs used in the third trimester should not be continued in the first three months postpartum without any alterations in the dosages. Some patients would experience exacerbation of seizures during this period, which was attributable to sleep deprivation and physical exhaustion. It is helpful to arrange with the family members to share some aspects of caring for the newborn to avoid undue physical and emotional stress.

Breast feeding

Most of the AEDs tend to cross in to the breast milk in inverse relation to their protein binding . Newer AEDs tend to pass in to breast milk in greater concentration than older drugs. The benefits of breast-feeding probably far outweigh the potential risk to the infant. Nevertheless, infants need to be carefully monitored for any untoward effects attributable to AED exposure through breast milk. Monitoring of infant serum drug concentrations is advisable but not mandatory. The general recommendation is to continue breastfeeding, but the feeds may be given before the woman takes her AED doses[4].

AMERICAN ACADEMY OF NEUROLOGY RECOMMENDATIONS

The American academy of neurology(AAN) has also released comprehensive clinical guidelines for the management of women with epilepsy during pregnancy. These guidelines first formulated in 1998 are now being updated[35].

WWE during reproductive years

The following recommendations are proposed as guidelines

- The choice of AED for WWE during their reproductive years should be that deemed most appropriate for seizure type.
- Monotherapy should be the aim of treatment.
- The decrease in effectiveness of hormonal contraception observed in WWE taking enzyme-inducing AEDs must be discussed with all WWE as they enter reproductive years.
- In light of known pregnancy patterns (high rate of unplanned pregnancies and late provider contact), folic acid supplementation should be instituted in WWE with no less than 0.4 mg per day and continued through pregnancy.

WWE during and after pregnancy

The following recommendations are proposed as guidelines:

- AED therapy for WWE should be optimized before conception if possible. If AED withdrawal is planned, this should be completed at least 6 months before conception. Change to an alternate AED should not be undertaken during pregnancy for the sole purpose of reducing teratogenic risk.
- WWE, especially those treated with carbamazepine,divalproex sodium, or valproic acid, should be offered prenatal testing with alpha-fetoprotein levels at 14 to 16 weeks' gestation, Level I1 (structural)ultrasound at 16 to 20 weeks' gestation, and, if appropriate, amniocentesis for amniotic fluid alpha-fetoprotein and acetylcholinesterase levels.
- Breast-feeding is not contraindicated in WWE taking AEDs; however, for WWE taking sedating AEDs, the neonate must be monitored for sedation.

The following recommendations are proposed as practice options:

- Non-protein-bound AED levels should be monitored during pregnancy. For the stable patient, levels should be ascertained before conception, at the beginning of each trimester, and in the last month of pregnancy. Additional levels should be done when clinically indicated (seizure occurrence, side effects, suspected noncompliance).
- AED levels should be monitored through the eighth postpartum week. If AED dosage increases have been necessary during pregnancy, subsequent reductions to the prepregnancy dosage will usually be possible and may be necessary to avoid toxicity.
- Vitamin K, 10 mg per day, should be prescribed in the last month of pregnancy to WWE taking enzyme-inducing AEDs. If this has not been done, parenteral vitamin K, should be administered toWWE as soon as possible after the onset of labor.

Note: This recommendation does not supplant the ACOG/AAP recommendation for the administration of 1 mg vitamin K, to the neonate.

Recommendations for future research

- There remains a need for well-designed studies of pregnancy outcomes for WWE, especially in light of the availability of several new AEDs.
- A study of the efficacy of hormonal contraception in WWE is needed in order that those requiring AEDs can be appropriately counseled regarding optimal birth control methods.
- Investigation of the complex issues surrounding seizure frequency changes through the stages of reproductive life and with cyclic hormonal fluctuations over the menstrual cycle is necessary.
- Further research into genetic markers that may predict a susceptibility to the teratogenic effects of AEDs may help guide primary and secondary preventive efforts.
- Ethical issues surrounding testing of AEDs in women during reproductive years must be explored and addressed.
- Endorsement and promotion of pregnancy registries to monitor AED teratogenesis should be undertaken by professional organizations of health care providers involved in the care of WWE.

MATERIALS AND METHODS

Criteria for patient selection

- This study includes women with epilepsy already registered at the epilepsy clinic of the Government Stanley hospital, Chennai.
- Patients were included in the study when pregnancy was first reported.

Exclusion criteria

- Patients changing antiepileptic drugs during the course of the study were excluded.

Methodology

This is an observational study involving women with epilepsy undergoing regular treatment at the epilepsy clinic of the department of neurology of the Government Stanley hospital. It addresses various issues faced by epileptic women during and after pregnancy.

- Pregnant women with epilepsy are included in the study when pregnancy is first reported.

- Data regarding seizure type, antiepileptic drug used, seizure frequency, folate supplementation is collected using a proforma based on the EURAP pregnancy registry proforma during the first visit. The patient is also counseled about various aspects of pregnancy in epileptics.
- Patient is followed up through monthly visits to the epilepsy clinic. Biochemical screening in the form of serum alpha feto protein level is done by the 12-14th week of gestation. Ultrasound scan for foetal anomalies is done during the 16-18th week of pregnancy.
- After delivery data is collected regarding outcome, intrapartum seizures, mode of delivery using a proforma. The baby is examined for growth retardation as well as congenital malformations.

Maternal serum alpha feto protein

AFP is a glycoprotein produced first by the yolk sac and then by the foetal liver. It reaches its maximum by 10 to 13 weeks of gestation, then declines to <100µg/L by term. It is usually reported as multiple of median (MoM) to minimize interlaboratory variability and adjust for patients' weight, gestational age and twin pregnancies. It is a valuable screening test in various conditions. This study uses this test as an early screen for neural tube defects which are known to be associated with antiepileltic drug use[37].

Levels are increased in

- Open neural tube defects(detects 80% of severe cases)
- Ventral wall defects – gastroschisis, omphalocoele
- Multiple pregnancy
- Intra uterine death
- Esophageal or duodenal atresia
- Cystic hygroma
- Renal disorders – agenesis, polycystic kidneys, urethral obstruction
- Turners syndrome
- Oligohydramnios
- Placental causes – infarction,thrombosis

Levels are decreased in

- Downs syndrome, Edwards syndrome
- Long standing foetal death
- Overestimation of gestational age
- Increased maternal weight, diabetes mellitus

PROFORMA

A detailed history was recorded as per the following proforma

- Name:
- Age :
- Address:
- Registration number:
- Education/occupation:
- Seizure type:
- Seizure etiology:
- Seizure history(pre pregnancy) : Seizure frequency

AED used and dose

- Obstretic history: Gravida

Para

Abortions

- LMP:
- Duration of pregnancy when first reported:
- EDD:

- Spontaneous abortion/MTP: yes/no
- Radiation exposure: yes/no
- Pregnancy details – therapy

	AED	Dose	Folic acid	Dose
1st trimester				
2nd trimester				
3rd trimester				

- Pregnancy details – epilepsy

	Seizure frequency	Status epilepticus	Non convulsive seizures
1st trimester			
2nd trimester			
3rd trimester			

- Alpha feto protein level:
- Structural ultrasound: Date

  Report
- Date of delivery:
- Intra partum seizures: Yes/No
- Intra partum status epilepticus: Yes/No
- Other complications of pregnancy, specify:
- Mode of delivery:

- Comments reg mode of delivery:
- Birth weight:
- Congenital malformations: Yes/No

  Specify type
- Perinatal mortality: Yes/No

  Specify cause
- Infant mortality: Yes/No

  Specify cause
- Developmental milestones:

OBSERVATIONS AND ANALYSIS

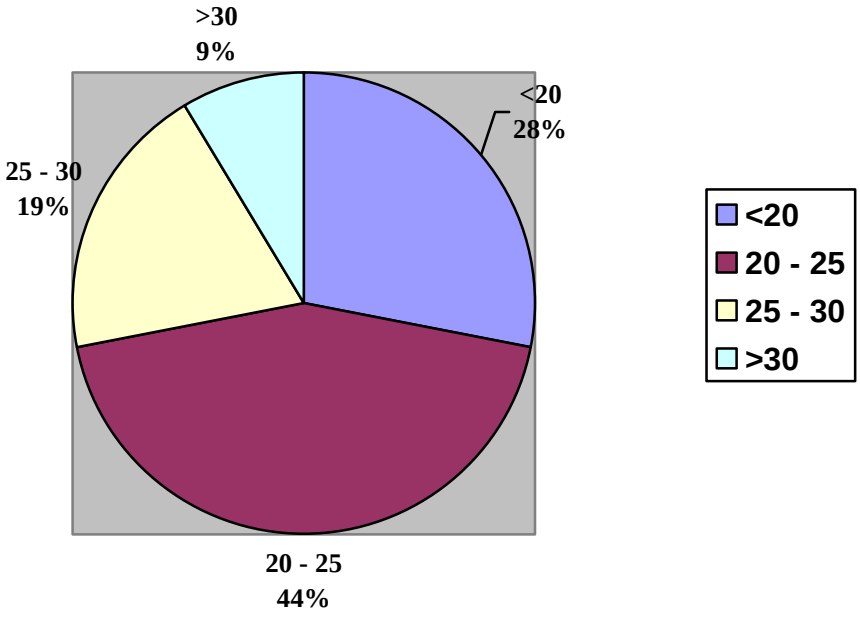
This study was conducted in Government Stanley hospital during the years 2007-2008. A total of 93 women with epilepsy were enrolled and followed up. All patients were already on treatment at the epilepsy clinic at the time of inclusion into the study. Patients who changed anti epileptic drugs during the course of pregnancy were excluded from the study.

- Total number of study subjects: 93
- Age

The age of the patients ranged from a minimum of 17yrs to a maximum of 34yrs. The mean age was 23.75yrs. The age distribution is as follows.

<20 years	-	26 patients
20 to 25years	-	41 patients
25 to 30years	-	18 patients
>30years	-	8 patients

AGE DISTRIBUTION



- **Type of epilepsy**

Of the 93 patients in the study, a majority of 67 patients (73%) had generalized tonic clonic seizures. 25 patients had partial seizures, either simple or complex. 1 patient had juvenile myoclonic epilepsy.

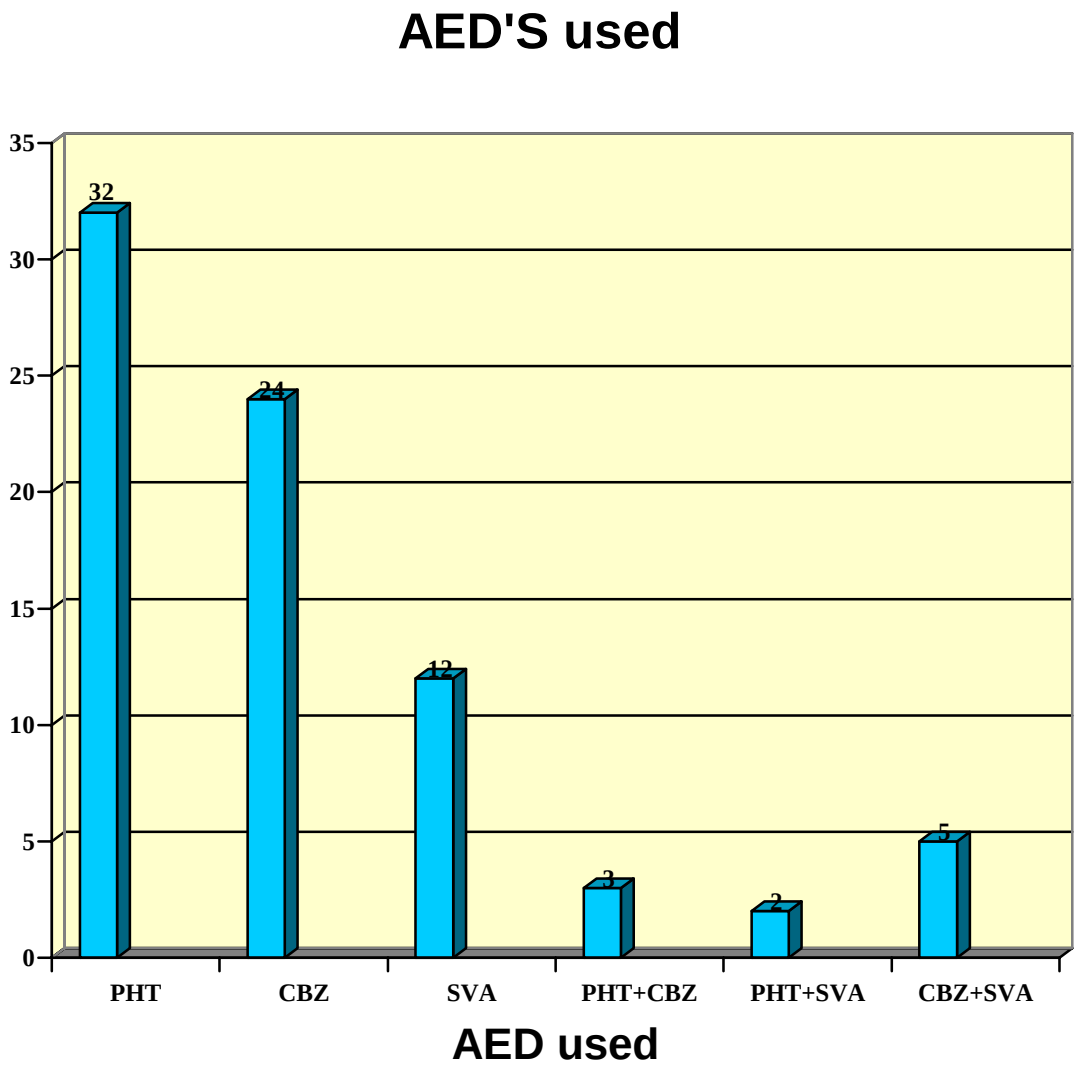
- **Obstetric status**

The study included primigravidas as well as multigravidas. 45 patients were primis. 48 patients were multigravidas.

- **Antiepileptic drug used**

The older antiepileptic drugs mainly – phenytoin, carbamazepine, and sodium valproate are the ones being used at the epilepsy clinic of the Government Stanley hospital. They are used either singly or in combination. Appropriate drugs are given for epilepsy syndromes. But the use of newer antiepileptic drugs is rare. The patients in this study were on the following drugs-

Phenytoin(PHT)	-	32 patients (34%)
Carbamazepine(CBZ)	-	24 patients (25.5%)
Sodium valproate(SVA)	-	12 patients (12.8%)
PHT + CBZ	-	3 patients (3.2%)
PHT + SVA	-	2 patients (2.1%)
CBZ + SVA	-	5 patients (5.3%)



Folic acid supplementation in the first trimester

Patients who reported pregnancy to the epilepsy clinic were all prescribed folic acid tablets. These tablets contained 1mg of folic acid. However it was observed that a large number of patients reported their pregnancy late and hence did not take folic acid supplementation during the first trimester. Another subset of patients had been taking 5mg folic acid tablets as prescribed by their Obstetrician.

Folic acid (1mg) - 45 patients

Folic acid (5mg) - 13 patients

No folic acid - 35 patients

- **Seizures during pregnancy**

The majority of patients had an uneventful seizure free pregnancy. 19 patients (20.1%) had seizures during the first trimester. 13 patients (13.9%) had seizures during the second and third trimesters. It was observed that patients with poorly controlled seizures in the preconceptional period continued to have seizures even during pregnancy.

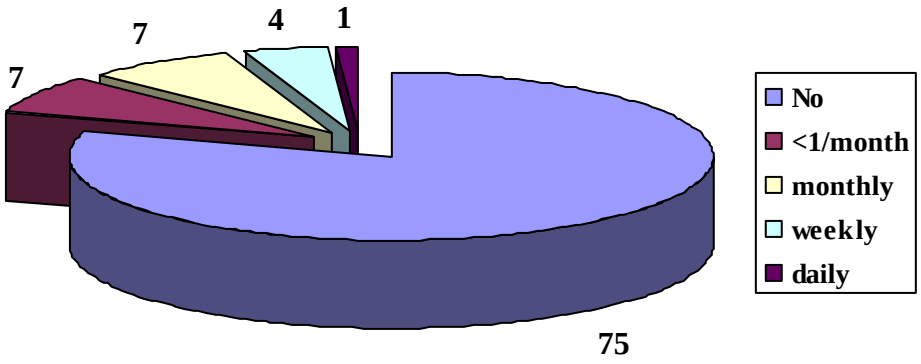
Seizure frequency in the first trimester is as follows:

Seizure frequency	Number of patients	Percentage
No seizures	75	79.8
< 1/month	7	7.4
monthly	7	7.4
weekly	4	4.2
daily	1	1.1

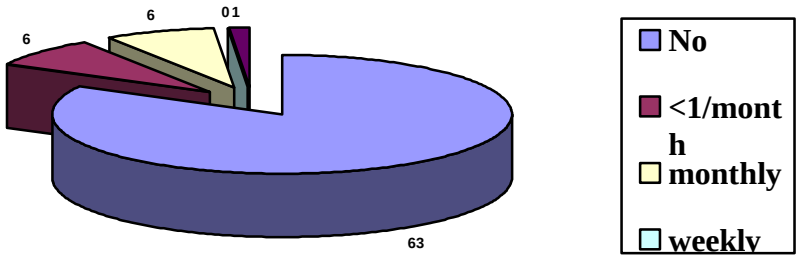
Seizure frequency in the second and third trimester is as follows:

Seizure frequency	Number of patients	Percentage
No seizures	63	67
<1/month	6	6.4
Monthly	6	6.4
Weekly	0	0
Daily	1	1.1

Seizure frequency - 1st trimester



Seizure frequency - 2nd trimester



- **Incidence of status epilepticus**

2 patients presented with an episode of status epilepticus each in the first trimester.

One patient had generalized tonic clonic seizures and was on treatment with phenytoin. She had an increased frequency of seizures in the first trimester with 2-3 episodes/week. Seizure frequency decreased in later trimesters, she did not have intrapartum seizures. She had a normal vaginal delivery and the baby was normal.

The second patient also had generalized tonic clonic seizures and was on phenytoin. She had 3-4 episodes of seizures weekly in the first trimester. She had a spontaneous abortion following status.

Both these patients had poor seizure control preconceptionally.

- **Intrapartum seizures**

A total of 4 patients had seizures during delivery. The details are as follows:

Sl. No	Seizures in 1st trimester	Seizures in 2nd, 3rd trimester	AED used	Mode of delivery	Comments
1.	No	Monthly	CBZ	Normal	Normal baby
2.	Monthly	Weekly	SVA	Operative	Normal baby
3.	No	Weekly	SVA+CBZ	Operative	Normal baby
4.	No	No	SVA+CBZ	Operative	Normal baby

It was observed that incidence of intrapartum seizures was higher in patients who reported seizures during the 2nd ,3rd trimesters. Three of these patients had an increased seizure frequency in the later part of pregnancy as compared to the 1st trimester. Intrapartum seizures also constituted an important indication for operative deliveries as three of the four patients ultimately underwent cesarian sections. All these three patients were on treatment with valproate.

Three of these patients had primary generalized seizures. One had complex partial seizure with secondary generalization.

- **Incidence of spontaneous abortions**

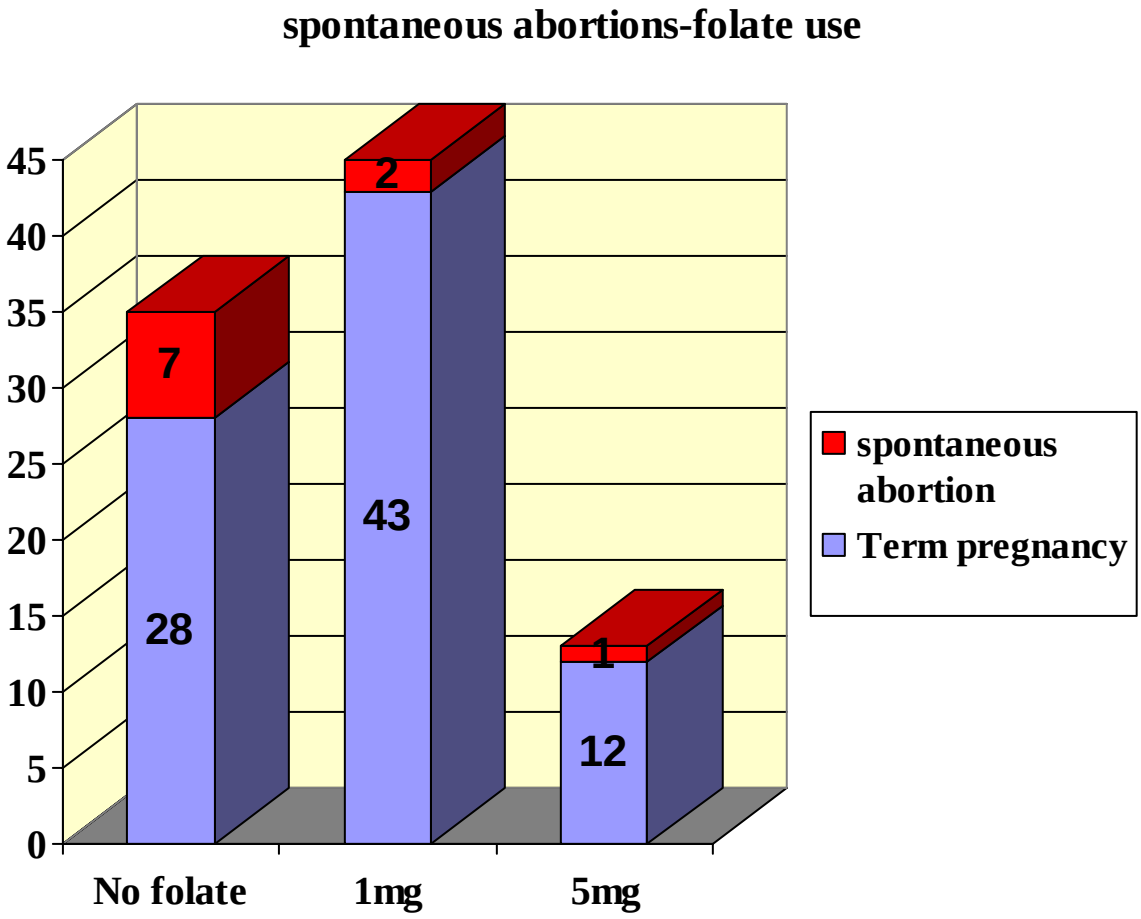
Spontaneous abortion was observed in 10 patients (10.6%). A significant correlation was observed between occurance of seizures in the first trimester and increased incidence of spontaneous abortions.

A p value of 0.04 was obtained.

		Spontaneous abortion			
		No		Yes	
		n	%	n	%
Seizures in 1st trimester	No	67	80.7%	7	70.0%
	yes	16	19.3%	3	30.0%

A significant correlation was also observed between spontaneous abortions and folate supplementation.

7 of the 10 patients who had spontaneous abortions had not received folate supplementation in the first trimester. 2 had received 1mg of folic acid and 1 patient had received 5mg of folic acid.



It was observed that of the 35 patients who did not receive folate, 7 patients – 20% had spontaneous abortions. Of the 45 patients who received folate 2 patients – 4.4% had spontaneous abortions. This figure was 1- 7.6% among the group of 13 patients on 5mg of folate.

- **Mode of delivery**

16 out of a total of 64 patients who reached term underwent operative deliveries. There is an increased incidence of operative deliveries in women with epilepsy as compared to the hospital average for controls. It is statistically significant with a p value of 0.04.

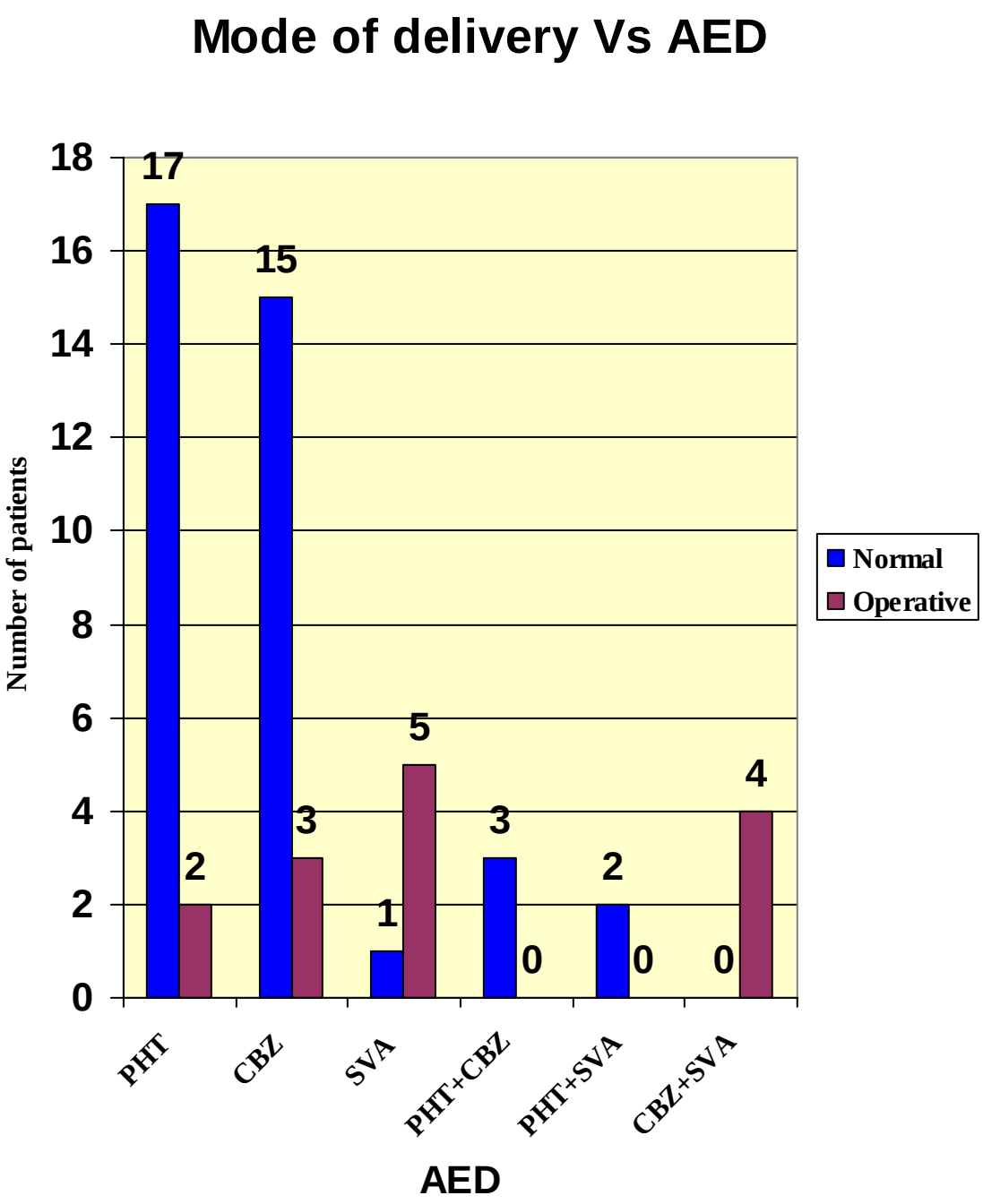
This data is represented in the following table

	Study	control
Incidence of operative delivery	25%	15%
sample size	64	10,000

P = 0.04

The indication for operative delivery was fetal distress in 2 patients, intrapartum seizures in 3 patients, post dated pregnancy in 6 patients, malposition in 1 patient and previous LSCS in 2 patients.

Sodium valproate use was observed to be associated with higher incidence of operative deliveries. Of the 6 patients who were on sodium valproate at the time of delivery 5 underwent operative deliveries. All 4 patients who were on a combination of sodium valproate and carbamazepine had operative deliveries.


Mode of delivery Vs AED
Number of patients
18
16
14
12
10
8
6
4
2
0
17
2
15
3
1
5
3
0
2
0
0
4
Normal
Operative
PHT
CBZ
SVA
PHT+CBZ
PHT+SVA
CBZ+SVA
AED

- **malformations**

Only one major congenital malformation was seen. The baby had a cleft lip and palate(1.6%). The mother had been on monotherapy with sodium valproate. She had not been on folic acid supplementation.

- **Low birth weight**

16 out of 64 babies (25%) were low birth weight and weighed under 2500gm.

- **Perinatal mortality**

1 baby(1.1%) was still born at 36weeks of gestation. Cause was not ascertained.

DISCUSSION

This study followed 93 pregnancies in women with epilepsy, the following observations were made

Seizures during pregnancy in women with epilepsy

Of the 93 pregnancies followed, a majority of 74 (79.8%) were seizure free throughout. 19 patients (20%) had seizures in the first trimester. 13 patients (13.9%) had seizures in the second and third trimesters. Factors that could have been associated with seizures are poor seizure control even before pregnancy, deliberate non compliance with anti epileptic drug intake, sleep deprivation and decreased blood levels of anti epileptic drugs during pregnancy.

Similar seizure frequency was seen in a study by **Endo.S et al**[26], who reported a seizure frequency of 19.4%.

A frequency of 30% was seen in a study by **Bunyan et al**[30]**.**

Another study by **Vajda et al**[23] reported a seizure frequency of 49%. Epilepsies that were active in the year before pregnancy tended to have increased risk of seizures during pregnancy.

Intrapartum seizures

In this study 4 patients(6.3%) of the 64 patients who reached term developed intrapartum seizures. 3 of these patients had primary generalized seizures and 1 had complex partial seizure with secondary generalization. Intrapartum seizures were not observed in patients with simple partial seizures. Correlation was seen between increased seizure frequency in the third trimester and intrapartum seizures in 3 patients. Intrapartum seizures also observed to lead to increased frequency of operative delivery with 3 of our patients requiring caesarian sections.

Studies by the **EURAP study group**[22] showed an intrapartum seizure frequency of 3.5%. Intrapartum seizures were more common in women who had seizures during pregnancy. A study by **Richmond et al**[28] also supports this observation.

Katz et al[27] reported an intrapartum seizure frequency of 12.5%. All of these patients had generalized epilepsies as in our study. 3 out of 4 patients had subtherapeutic anti epileptic drug levels.

Spontaneous abortions

10 patients (10.6%) had spontaneous abortions. 7 out of these 10 patients had not received folic acid supplementation. A positive correlation was observed between occurrence of seizures in the first trimester and spontaneous abortions with a p value of <0.04.

Studies by **Richmond et al**[28]**, Schupf et al**[32] **and Goel et al**[29] all show increased incidence of spontaneous abortion in women with epilepsy. The reasons for this observation are – the effect of anti epileptic drug intake, effect of seizures on gonadotropin levels. Some studies have also shown an association of low folate levels with increased incidence of spontaneous abortion.

Mode of delivery

This study showed an increased incidence of operative deliveries. 16 patients (25%) underwent caesarian sections. This was statistically significant with a p value of 0.04. There was a positive correlation with anti epileptic drug polytherapy, especially with the use of sodium valproate.

An Indian study by **Thomas et al**[31] showed similar results with a one third incidence of operative delivery. A study by **Richmond et al**[28] showed no significant increase in operative deliveries, but showed an increase in the

number of patients needing induction of labor. Overall most studies show an increase in the interventions done during delivery in women with epilepsy.

Folic acid supplementation

62% of our patients had received folic acid supplementation. The dosage varied from 1 to 5 mg with 59% of patients taking 1mg. This compares with the situation in developed countries where 64 t0 78% of patients receive folic acid supplementation – **Seale et al**[34]**.**

An Indian study by **Thomas et al** [31] reported a 40% use of folic acid.

Our study also shows an increase in incidence of spontaneous abortions in women who have not received folic acid.

Adverse outcomes of pregnancy in women with epilepsy

Low birth weight was the commonest adverse outcome seen in our study. 25% of neonates were low birth weight. This value is in concordance with the 21% incidence of low birth weight observed by **Thomas et al** [31]**.**

An incidence of 18% was observed by **Goel et al** [29]**.** A Saudi Arabian study by **Bunyan et al**[30] showed an incidence of 9%. The incidence in developed countries ranges from 7 to 10% - **Sivgos et al.**

Economic and social factors also probably contribute to the increased incidence seen in our country.

Only one major congenital malformation was seen in this study (1.6%). One neonate had a cleft lip and palate. The mother was on 800mg/day of sodium valproate for generalized tonic clonic seizures. She had not received folic acid.

Orofacial clefts constitute 30% of all major congenital malformations – **Kelly et al.** An Indian study by **Goel et al**[29] with 37 patients reported no congenital malformations. On the other hand another Indian study by **Thomas et al** [31] reported an incidence of 12.5%.

Most studies show the risk of congenital malformations in infants of epileptic women to range from 3 to 10% - **Tomson et al**[3]**.** The risk may increase to up to 17% with polytherapy – **Crawford et al**[4]**.**

CONCLUSION

In a study of 93 pregnancies in women with epilepsy it was found that:

1. A majority of 79.8% were seizure free. 20% had seizures in first trimester and this figure diminished to 13.9% later in the course of pregnancy.
2. Intrapartum seizures were seen to be related to:
    a. Seizures in the third trimester
    b. Generalized type of seizure disorder
    c. Increased incidence of operative delivery
3. An increased incidence of spontaneous abortions was seen in women with epilepsy. This was found to correlate with seizures in the first trimester and also with a lack of folic acid supplementation.
4. There was an increased incidence of operative deliveries in women with epilepsy. This was associated with polytherapy especially including sodium valproate.

5. Only 62% of patients received folic acid supplementation. Incidence of complications like spontaneous abortions were higher in patients not receiving folic acid.
6. Low birth weight is the commonest adverse neonatal outcome.

BIBLIOGRAPHY

1. Battino D, Tomson T. Management of epilepsy during pregnancy. Drugs. 2007;67(18): 2727-46.
2. Thomas S V. Management of epilepsy and pregnancy. Postgraduate Medicine. 2006 Jan-Mar; 52(1): 57-64.
3. Tomston T, Perucca E, Battino D. Navigating toward fetal and maternal health: the challenge of treating epilepsy in pregnancy; Epilepsia. 2004 Oct; 45(16): 1171-5.
4. Crawford P. Best practice guidelines for the management of women with epilepsy; Epilepsia. 2005; 46: 117-24.
5. Adab N, Tudur S C, Vinsten J, Williamson P. Common antiepileptic drugs in pregnancy in women with epilepsy. Cochrane Database syst rev. 2004; (3): CD004848.
6. Chang S I, McAuley J W. Pharmacotherapeutic issues for women of childbearing age with epilepsy. Annals of Pharmacotherapy. 1998 Jul-Aug; 32: 794-801.
7. Schmidt D, Canger R, Avanzini G, Battino D,Cusi C. Change of seizure frequency in pregnant epileptic women. J Neurol Neurosurg psychiatry. 1983 Aug; 46(8): 751-5.
8. Cleland P G. Risk benefit assessment of anticonvulsants in women of child bearing potential. Drug safety. 1991 Jan-Feb; 6(1): 70-81.

9. Genton P, Semah F, Trinka E. Valproic acid in epilepsy-pregnancy related issues. Drug safety. 2006; 29(1).
10. Brodtkorb E, Reimers A. Seizure control and pharmacokinetics of antiepileptic drugs in pregnant women with epilepsy. Seizure. 2008 Mar; 17(2): 160-5.
11. Kalviainen R, Tomson T. Optimizing treatment of pregnancy during epilepsy. Neurology. 2006 Dec 26; 67(12 suppl 4): S59-63.
12. Pimentel J. Current issues on epileptic women. Curr Pharm Des. 2000 May; 6(8): 865-72.
13. Pennel P B. 2005 AES annual course: evidence used to treat women with epilepsy. Epilepsia. 2006; 47 suppl 1: 46-53.
14. Pennel P B. The importance of monotherapy in pregnancy. Neurology. 2003 Jun 10; 60(11 suppl 4): S31-8.
15. Vajda F J, Hitchcock A, Graham J, Solim S C, O'brien T J. Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. 2006 Jun; 13(6): 645-54.
16. Adab N, Kini U, Vinten J, Ayres J, Baker G. The longer term outcome of children born to mothers with epilepsy. Journal of Neurology Neurosurgery and Psychiatry. 2004 Nov; 75(11): 1575-83.

17. Morrel M J. The new antiepileptic drugs and women: efficacy, reproductive health, pregnancy and foetal outcome. Epilepsia. 1996; 37suppl 6: S 34-44.
18. Perruca E. Pharmacological and therapeutic properties of valproate: A summary after 33 years of clinical experience. CNS drugs. 2002; 16(10): 695-714
19. Wilson R D, Johnson J A, Wyatt P, Allen V, Gagnon A. Preconceptional vitamin/ folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J obstretics Gynaecology Can. 2007 Dec; 29(12): 1003-26.
20. Eadie M J, Vajda F J. Should valproate be taken during pregnancy?; Therapy and clinical risk management. 2005 March; 1(1): 21-6
21. Harden C L. Pregnancy and epilepsy. Semin Neurology. 2007 Nov; 27(5): 453-9
22. EURAP study group. Seizure control and treatment in pregnancy: Observations from the EURAP epilepsy pregnancy registry. Neurology. 2006 Feb 14; 66(3): 354-60.

23. Vajda F J, Hitchcock A, Graham J, O'Brien T. Seizure control in antiepileptic drug treated pregnancy; Epilepsia. 2008 Jan; 49(1): 172-6.
24. Meador K J, Baker G A, Finnel R H, Kalayjian L A, Li porace J D. In utero antiepileptic drug exposure: fetal death and malformations. Neurology. 2006 Aug 8; 67(3): 407-12.
25. Tomson T, Battino D. Teratogenic effects of anti epileptic drugs. Seizure. 2008 Mar; 17(2): 166-71.
26. Endo S, Hagimoto H, Yamazawa H, Kajiharas. Statistics on deliveries of mothers with epilepsy at Yokohama city university hospital. Epilepsia. 2004; 45 suppl: 42-7.
27. Jeffrey M. Katz, Orrin Devinsky. Primary generalized epilepsy: a risk factor for seizures in labour and delivery? Seizure. 2003; 12: 217-219.
28. Jane R Richmond, Preetha Krishnamoorthy, Eva Andermann. Epilepsy and pregnancy: An obstretic perspective. American journal of obstretics and gynaecology. 2004; 190: 371-9.
29. Poonam Goel. Lagya Devi, Pradip Kumar Saha. Maternal and perinatal outcome in pregnancy with epilepsy. The Internet Journal of Gynaecology and Obstretics. 2006; Vol 5: No 2.

30. Muneera A L Bunyan, Zainab Abo-Talib. Outcomes of pregnancies in epileptic women: a study in Saudi Arabia. Seizure 1999; 8: 26-29.
31. Thomas S V, Indrani G, Devi G C et al. Pregnancy in women with epilepsy: Preliminary results of Kerala registry of epilepsy and pregnancy. Neurology India 2001; 49: 60-66.
32. Nicole Schupf, Ruth ottoman. Risk of epilepsy: Association with maternal abortion. Neurology. Nov 2001; 57: 1642-49.
33. Sharma R R: Pregnancy, epilepsy and pharmacotherapy. J post grad Med. 1987; 33: 163.
34. Seale C G, Morrel M J, Nelson L et al. Analysis of prenatal and gestational care given to women with epilepsy. Neurology. 1998; 51: 1039-1045.
35. American academy of neurology. Practice parameter: Management issues for women with epilepsy. Report of the quality standard subcommittee of the American academy of neurology. Neurology. 1998; 51: 944-948.
36. Bertram G Katzung, Roger J porter. Antiseizure drugs: Basic and clinical pharmacology; 395-418.
37. Jacques Wallach. Prenatal screening and diagnosis: Interpretation of diagnostic tests; 644-645.

38. Cole H M. Chorionic villus sampling: a reassessment. Diagnostic and therapeutic technology assessment. JAMA. 1990; 263: 305.
39. Vazquez B, Gibson P, Kustra R. Epilepsy and women's health issues: unmet needs- survey results from women with epilepsy. Epilepsy behaviour. 2007 Feb; 10(1): 163-9.
40. Montouris G. Safety of the newer anti epileptic drug oxcarbazepine during pregnancy. Current Medical Research opinions. 2005 May;21(5):695 – 701.

Key to master chart

A. Name of patient

B. Surname

C. Last menstrual period

D. Age of the patient

E. Education: Graduate 1

High school 2

Primary school 3

Illiterate 4

F. Radiation exposure during pregnancy

G. Gravida

H. Parity

I. Type of epilepsy: GTCS 1

Partial 2

J. Etiology: Idiopathic 1

Symptomatic 2

K. Spontaneous abortion: No 0

Yes 1

L. Induced termination of pregnancy: No 0

Yes 1

M. Expected date of delivery

N. Preg. dur: duration of pregnancy when first reported

O. Folate supplementation: No 0

1 mg 1

5 mg 2

P. Anti epileptic drug used in first trimester

Phenytoin 1

Carbamazepine 2

Sodium valproate 3

PHT+CBZ 4

PHT+SVA 5

SVA+CBZ 6

Q. Dose of AED in first trimester

R. Peak dose of AED

S. Seizures in the first trimester: No 0

<1/month 1

Monthly 2

Weekly 3

>weekly 4, daily 5

T. Status epilepticus in first trimester: No 0

Convulsive 1

Nonconvulsive 2

U. Still birth : No 0

Yes 1

V.AED use in second trimester: No 0

Yes 1

W. Seizures in second trimester

X. Status epilepticus in second trimester

Y. Malformation directed ultrasound: Not done 0
Normal 1
Abnormal 2

Z. Alpha feto protein: Normal 1
Increased 2
Decreased 3

AA. AFP levels in ng/ml

AB. AED use in third trimester: No 0
Yes 1

AC. Seizures in the third trimester

AD. Status epilepticus in third trimester

AE. Mode of delivery: Normal vaginal 1
Forceps/vaccum 2
LSCS 3

AF. Intrapartum seizures: No 0
Yes 1

AG. Birth weight of neonate in grams

AH. Perinatal death: No 0
Yes 1

AI. Congenital malformations